What is the appropriate dialysate calcium concentration for the dialysis patient?

E. Ritz\(^1\), J. Passlick-Deetjen\(^2\) and J. Lippert\(^1\)

\(^1\)Department of Internal Medicine, Ruperto Carola University, Heidelberg, and \(^2\)Fresenius AG, Bad Homburg, Germany

Abstract. Recently, there has been a trend to lower dialysate calcium concentrations because of the frequent occurrence of hypercalcaemia with the use of calcium-containing phosphate binders. No single dialysate calcium concentration is available which suits all dialysis patients. The risk of hypercalcaemia depends on intradialytic (diffusive and convective) calcium transport and interdialytic calcium balance (negative or positive intestinal balance). Low dialysate calcium concentrations expose the patient to the risks of negative calcium balance and increase in parathyroid hormone concentration, particularly if patients are non-compliant with the intake of calcium-containing phosphate binders.

Key words: dialysate calcium; hyperparathyroidism; hypercalcaemia; calcium balance

Introduction

In discussing the issue of dialysate calcium concentration, it is useful to put things into historical perspective.

Dialysis fluid calcium concentrations were selected in the pioneer era by reasoning that values close to the normal concentration of diffusible calcium were appropriate. The recognition of the role of hypocalcaemia in the genesis of hyperparathyroidism [1], particularly following the elegant studies of the Mayo Clinic [2], led to the selection of increased concentrations of calcium in the dialysate, i.e. 1.75 mmol/l. This remained the standard for a long time, but recently low dialysate calcium concentrations have grown in popularity [3].

The explanation for the trend is obvious. The recognition of the toxic effects of aluminium has led to the use of calcium salts as the sole phosphate-binding agents [4]. In this effort, hypercalcaemia has become the limiting factor for the administration of calcium carbonate. Hypercalcaemia is observed in a considerable proportion of patients, particularly those with low bone turnover [5]. The risk of hypercalcaemia is further increased by treatment with active vitamin D metabolites.

An attractive strategy for preventing hypercalcaemia while continuing the benefit from the use of calcium carbonate as a phosphate-binding agent was to reduce the calcium concentration in the dialysate from 1.75 to the more 'physiological' concentration of 1.25 mmol/l or even less.

Epidemiological findings

What calcium concentrations are currently used in Europe? The 1993 EDTA report [6] shows that a dialysate calcium concentration of 1.75 mmol/l or more on haemodialysis is still used exclusively in more than half of the centres, but a sizeable proportion, approx. 40%, use 1.5–1.74 mmol/l in most patients and almost 10% use less than 1.25 mmol/l in most or some patients. As a complicating factor, many patients receive active vitamin D metabolites, i.e. 42% of the total population evaluated by the registry. The preferred mode of administration continues to be continuous oral administration, i.e. 85%, while a variable proportion selects intravenous or other modes.

Table 1 shows that in the Heidelberg centre haemodialysis population, 1.75 mmol/l is the preferred dialysate calcium concentration, only a minority using 1.25 mmol/l. Ninety per cent of the patients are on calcium-containing phosphate binders (only 20% of the patients self-select calcium acetate when given the choice as is done in our unit); unfortunately, adjunctive aluminium-containing compounds are still required in 31% of the patients, although it is rare that hypercalcaemia precludes the use of calcium-containing phosphate binders altogether and necessitates aluminium salts as monotherapy. With this regime, almost all patients are normocalcaemic. The highest aluminium concentration is 80 µg/l and parathyroid hormone (PTH) tends to be well controlled, the median being 8.7 pmol/l and the maximum 107 pmol/l.

© 1996 European Dialysis and Transplant Association–European Renal Association
positive transmembrane calcium flux is seen at dialysate positive intradialytic calcium balance. The calcium balance of the patient has to be offset by a neutral overall balance, the negative interdialytic calcium entering the gut via intestinal secretion is lost in faeces. Johnson [2] reasoned that in order to achieve a calcium deficit of 50 g if it remained uncorrected. How much calcium per day is required to avoid negative calcium balance? In the patient who receives no oral calcium i.e. low-calcium diets. Kopple and Coburn [7] showed in the interdialytic interval? In the patient who receives no oral calcium D-dependent active transport is defective so that calcium transport out of the intestinal lumen via vitamin D-dependent active transport is defective so that calcium concentration gradient of diffusible calcium, i.e. the sum of ionized and complexed calcium (citrate and phosphate, the concentrations of which are altered in renal failure without having a major impact on the proportion of complexed calcium); and (ii) the dialysate calcium concentration. It is important that ionized calcium in the dialysate (which was the only parameter measured in some reports) is lower than total calcium. Calcium transfer is also dependent in a minor way on the Donnan equilibrium. Convective calcium transport is often neglected or underestimated. Loss of 1 l of ultrafilterate causes a net loss of approx. 50 mg calcium. With 2 l of ultrafiltration per session, this loss would result in an annual calcium deficit of 50 g if it remained uncorrected.

How is calcium balance achieved in the interdialytic interval? In the patient who receives no oral calcium salts or active vitamin D metabolites, calcium balance in the interdialytic interval is negative on self-selected, i.e. low-calcium diets. Kopple and Coburn [7] showed that in such patients an intake of 1000-1500 mg calcium per day is required to avoid negative calcium balance. This is due to the fact that uphill calcium transport out of the intestinal lumen via vitamin D-dependent active transport is defective so that calcium entering the gut via intestinal secretion is lost in faeces. Johnson [2] reasoned that in order to achieve neutral overall balance, the negative interdialytic calcium balance of the patient has to be offset by a positive intradialytic calcium balance.

The recent study of Hou et al. [8] showed that positive tranmembrane calcium flux is seen at dialysate calcium concentrations of 1.75 mmol/l and 1.25 mmol/l, while negative calcium flux occurs with 0.75 mmol/l. With the low dialysate calcium concentration, because of a progressive reduction in plasma calcium concentration, the magnitude of negative calcium flux decreased with time, providing an element of self-correction, while positive calcium flux with high dialysate calcium concentrations continued unabated, progressively augmenting the risk of hypercalcaemia.
secretion and—although the relation between the two parameters is somewhat variable between patients—on bone turnover. Argilés et al. [9] showed an increase of mean intact PTH with time in patients on 1.25 mmol/l dialysate calcium who did not receive vitamin D treatment (Figure 1). So, apparently low dialysate calcium increases PTH, presumably via inducing a negative calcium balance. It appears a rational strategy to administer active vitamin D metabolites in an effort to prevent the increase of PTH. A study by Bouillon et al. [15] showed that increasing dialysate calcium to 7.5 mg/dl caused only a transient decrease of PTH concentration. When PTH concentration increased again, vitamin D was required to reverse such increase. The more potent effect of active vitamin D compared to dialysate calcium concentration has recently been confirmed by Argilés et al. [9]. iPTH concentration increased on low dialysate calcium, but this could be reversed when 1-α-hydroxy-vitamin D was administered. In CAPD patients, a tendency for an increase in PTH on low calcium concentrations in the peritoneal dialysis fluid was also noted in a recent multicentre prospective randomized controlled trial [16]. Weinreich et al. compared low (1.0 mmol/l) with standard (1.75 mmol/l) calcium concentration in CAPD patients. The lower calcium concentration in the dialysis fluid allowed to increase the average dose of calcium carbonate from 4.2 to 5.9 tablets per day, while the consumption of aluminium could be reduced from 1.1 to 0.7 tablets per day (Figure 2). All patients had 0.25 μg calcitriol per day. It is therefore of note that lowering of dialysate calcium did not cause a significant short-term change in PTH, although in the long run the proportion of patients experiencing an increase in iPTH was greater on low Ca. The usefulness of low calcium CAPD fluids has also been noted in other trials [17,18].

It follows that there is indeed a tendency for PTH to increase on low dialysate calcium, but that this trend can mostly be corrected by administration of active vitamin D metabolites. Nevertheless, monitoring of PTH concentration is necessary to identify early on those patients whose PTH tends to increase.

Calcium loss on zero calcium in the CAPD solution was approx. 400 mg/day [19] and cumulative calcium loss during a 4 h haemodialysis session using 0.75 mmol Ca/l was −5.8 mmol (232 mg) [8]. With more conventional low calcium fluids the amount of calcium lost is also not negligible, but it must be viewed in relation to the risk of hyperphosphataemia.

Another crucial aspect is long-term maintenance of skeletal mineral content at different dialysate calcium concentrations. It is reassuring that using the above regimen (Table 1) we in Heidelberg as well as Hutchinson in Manchester (personal communication) noted normal average calcium content in the vertebral bodies, i.e. within the expected range for age and gender. It is obvious that such measurements in the vertebral bodies may not detect regional differences in mineral content which may be substantial. Clearly more information on this point is required.

The issue is compounded by the fact that patients are frequently non-compliant. Hippocrates stated ‘... keep watch also on the faults of the patients which often make them lie about the taking of things properly'. As recently summarized by Wright et al. [20], non-compliance is universal, even in potentially life-threatening conditions such as tuberculosis, epilepsy, or leprosy.

What proportion of dialysis patients is non-compliant? Using electronic monitoring of pill boxes we found that less than 50% of our patients on dialysis take their medication. It follows that low-calcium dialysate is only safe in the long run if patients compensate diffusive and convective loss of calcium during dialysis by positive intestinal calcium balance between dialysis sessions, in other words if they take their calcium carbonate. The risk of negative calcium balance may be somewhat diminished by the administration of active vitamin D metabolites. Certainly, the ultimate solution would be the development of non-calcium-containing phosphate binders which would altogether eliminate the need to ingest oral calcium. In
calcium is a panacea, solving all problems of renal patients whose compliance with oral calcium salts seems sufficiently assured. We fully agree with the recent conclusion of Argilés [23] that use of low-calcium dialysate seems sufficiently assured.

Selection of dialysate calcium—cost/benefit considerations

The practical question remains: which dialysate calcium for whom? We fully agree with the recent conclusion of Argilés [23] that use of low-calcium dialysate must be individualized. It should be restricted to patients whose compliance with oral calcium salts seems sufficiently assured.

It would be naive to assume that low dialysate calcium is a panacea, solving all problems of renal bone disease. It is one, but only one, useful instrument in a concerted approach towards the management of renal bone disease. There are no free lunches, however, and there is a price to pay for the selection of low calcium fluids: the risk of increases of PTH concentrations and the risk of negative balance.

It is very likely, although still currently unproven, that the risk of an increase in PTH concentration depends on baseline parathyroid mass which one may perhaps be able to monitor in the future, using ultrasonography and MIBI scan. The potential risk of bone mineral loss (undesirable as it is) must be balanced against the risk of unopposed hyperparathyroidism.

Because the relation between PTH and bone turnover depends on baseline parathyroid mass which one may perhaps be able to monitor in the future, using ultrasonography and MIBI scan. Using such a cautious approach, the use of low-calcium dialysate should become safer in the future.

Limitations of low dialysate concentrations

How much is gained by lowering dialysate calcium; in other words, how much therapeutic leeway is provided by low dialysate calcium? In patients with vitamin D intoxication and patients on high doses of active vitamin D metabolites, low dialysate calcium concentrations have been tried, e.g. zero calcium peritoneal dialysate in patients with severe hypercalcaemia [19] and 1.0 mmol Ca/l in the dialysate in haemodialysed patients with severe hyperparathyroidism on 2.6 μg calciotril thrice weekly [21]. Nevertheless, the room for manoeuvre gained by manipulating the dialysate calcium concentration is somewhat limited. This is illustrated by the experience of Malberti et al. [22]. They reported on using zero calcium solutions in hyperparathyroid patients on CAPD receiving high calciotril treatment. Only in some patients did they observe a transient, and never sustained, decrease of PTH and four of the nine patients ultimately required parathyroidectomy.

References

11. Amann K, Ritz E. Cardiac structure and function in renal disease. Curr Opin (in press)
16. Weinreich T, Passlick-Deetjen J, Ritz E. Low dialysate calcium bone disease. It is one, but only one, useful instrument in a concerted approach towards the management of renal bone disease. There are no free lunches, however, and there is a price to pay for the selection of low calcium fluids: the risk of increases of PTH concentrations and the risk of negative balance.
Dialysate calcium


